

REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 1-24 are pending in the application.

Claims 3, 4, 5, 6, 15, 18 and 20 have been amended to address formal matters.

Claims 21-24 have been added. Support for new claims 21-24 may be found generally throughout the specification, the Examples, and original claim 3.

Applicants respectfully submit that no new matter has been added to the disclosure.

Claims 1-14 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Sawhney in view of Jeong. This rejection is traversed.

Sawhney proposes a two-phase hydrogel system to control the release rate of a drug. During preparation, Sawhney uses an oil-in-water-in oil emulsion with a macromer polymerized in the outside water phase. This oil-in-water-in-oil double emulsions basically serves to break the oil phase inside the water phase during emulsification. At the same time, hydrophobic substances migrate to the outside oil phase or accumulate on the outside surface of hydrogel microspheres as the hydrogel microspheres solidify through polymerization. As a result, the outside surface-associated hydrophobic substance may release very quickly and result in a burst effect.

In contrast, the present invention relates to a oil-in-water emulsion system in a bulky thermogelling hydrogel which forms in an aqueous environment. The soluble or entrapped substances in the oil phase tend not to migrate toward the outside aqueous hydrogel phase. Accordingly, when the hydrogel is solidified in situ, there is little to no burst effect observed.

In addition, thermogelling hydrogels cannot be implemented in the hydrogel system proposed by Sawhney because the thermogelling hydrogels usually have a phase transition temperature of 20-30°C. The gelling temperature must be around 37°C when a hydrogel forms in situ. However, after the polymer

is mixed with water to form the hydrogel, a preparation should be performed below phase transition temperature. The phase diagram shows that high temperatures causes an irreversible phase change and also may change the hydrogel. The phenomena (Syneresis temperature) also has been reported by Jeong (*Macromolecule* 33:8317-8322 (2000)).

Sawhney uses oil (or a fatty acid) as an internal oily phase which needs to be dissolved first in a hydrogel at elevated temperatures. Small droplets are then formed into a polymerized hydrogel as the temperature decreases. The preparation is opposite to that of a thermogelling hydrogel. In this regard, the concept of Sawhney is unable to be combined with thermogelling hydrogel to obtain the system of the present invention.

Thus, Sawhney, directed to a double emulsion preparation, would not have been able to achieve the same benefits exhibited by the present invention especially as it relates to the release profile (burst effect).

In an effort to remedy the deficiencies of Sawhney, the Official Action cites to Jeong. However, Applicants respectfully submit that the proposed combination of Sawhney in view of Jeong et al. fails to render obvious the claimed invention.

Jeong, (*Macromolecules* 2000, 33: 8317-8322) teaches poly(ethylene glycol) grafted with poly(lactic acid-co-glycolic acid) (PEG-g-PLGA). It is a polymer designed for a short-term (1-2 weeks) delivery system. However, this material shows a different drug profile as compared to PEG-PLGA-PEG or PLGA-g-PEG, as described at the second paragraph in right column on page 8317. Also, at the third paragraph in the left column on page 8322, Jeong states that the molecular structure of the polymers determines the extent of the drug release profile. Thus, one skilled in the art would have known that different hydrogel materials will have different drug release profiles. Accordingly, it cannot be said that one skilled in the art would have assumed that the effect of a hydrogel material could be inferred by observing other hydrogel materials, as suggested by the Official Action.

This is apparent upon considering the structural and functional properties of Jeong, the temperature-sensitive polymers of PEG-PLGA-PEG of the present invention (shown as formula (I)) in the specification, PEG-PLGA (shown as formula (II)) in the specification, and Poloxamer 407 (shown as formula (III)) in the specification. Among them, the molecular weight and the number of PEG and PLGA thereof are specifically defined on pages 5-6. The temperature sensitive polymers, PEG-PLGA-PEG, Poloxamer 407 and PEG-PLGA, exhibit different properties from PEG-g-PLGA taught by Jeong. Since the molecular structure of the polymers affect the extent of drug release profile as mentioned above, the long-term performance of the drug releasing system of the present invention which uses PEG-PLGA-PEG, Poloxamer 407 or PEG-PLGA as the temperature-sensitive polymer, can not be inferred from another drug releasing system using PEG-g-PLGA. The following shows the difference of the molecular structure between the hydrogel materials of the present invention (i.e. PEG-PLGA-PEG and PEG-PLGA) and Jeong (PEG-g-PLGA).

	Hydrogel material	Molecular structure
Present invention	PEG-PLGA	$\{ \text{PEG}-\text{PLGA}-\text{PEG}-\text{PLGA}-\text{PEG}-\text{PLGA} \}$
	PEG-PLGA-PEG	$\{ \text{PEG}-\text{PLGA}-\text{PEG}-\text{PEG}-\text{PLGA}-\text{PEG} \}$
D2	PEG-g-PLGA	$ \begin{array}{c} \text{PLGA} \quad \text{PLGA} \quad \text{PLGA} \\ \quad \quad \\ \{ \text{PEG}-\text{PEG}-\text{PEG}-\text{PEG}-\text{PEG}-\text{PEG} \} \\ \quad \quad \\ \text{PLGA} \quad \text{PLGA} \quad \text{PLGA} \end{array} $

The Table shows that the hydrogel material of Jeong is quite distinct from those of the present invention.

Furthermore, Sawhney does not demonstrate how long its drug releasing system performs. Thus, even if short-term PEG-g-PLGA taught by Jeong were used to replace the hydrogel material used in the drug delivery system of

Sawhney, the Official Action fails to provide any evidence that the combination would necessarily result in a long-term steady release of a drug, as provided by the claimed invention.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fastening element, either expressly or inherently.). >Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species).

In view of the above, Applicants respectfully submit that the position taken by the Official Action that the proposed combination of Sawhney and Jeong

would result in a delivery system as claimed is improper as a matter of law. There is no evidence to suggest that either Sawhney or Jeong expressly or inherently provides a delivery system with the features and properties of the claimed invention.

Furthermore, Applicants respectfully maintain that the claimed invention exhibits unexpected results. Indeed, the delivery systems of the claimed invention exhibit unexpected and unique properties (i.e., long-term sustained release) as compared to a hydrogel matrix (e.g., see Examples 9 and 10 of the present specification).

The Examiner is respectfully reminded that the Patent Office must consider objective indicia of nonobviousness whenever present. Specifically, the Patent Office is bound to consider evidence of unexpected results, commercial success, long-felt but unresolved needs, failure of others, skepticism of experts. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed Cir. 1983). Federal Circuit precedent mandates consideration of comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F.2d 1029 (Fed Cir. 1986). (Vacating Board decision which refused to consider data in the specification which compared an embodiment of the invention with the prior art product and noting that such evidence spoke to unexpected results and non-obviousness).

Thus, one skilled in the art would not have obtained the claimed invention with the proposed combination of Sawhney and Jeong and that the claimed invention exhibits unexpected and unique properties, Applicants respectfully submit that none of the pending claims are obvious.


Applicants respectfully request that the obviousness rejection be withdrawn.

Conclusion

In view of the present Amendment and foregoing Remarks, therefore, Applicants believe that the present application is condition for allowance at the time of the next Official Action. Allowance and passage to issuance is respectfully requested.

Respectfully submitted,

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